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Re: Interference
Patent
Attorney's Docket No. 008439-016

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Reissue Application of
U.S. Patent No. 4,775,624

Nils U. Bang et al

Application No.: 09/185,663

Filed: October 30, 1998

For: VECTORS AND COMPOUNDS
FOR EXPRESSION OF
HUMAN PROTEIN C

Group Art Unit: 164k

Examiner: Karen Carleson

REQUEST FOR INTERFERENCE PURSUANT TO 37 C.F.R. §1.607

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Applicants hereby request that an interference be declared between the instant application and U.S. Patent Nos. 5,302,529 and 4,968,626 to Foster et al. The information required by 37 C.F.R. §1.607(a) is set forth under headings which correspond to the subsections of §1.607 to facilitate consideration by the Examiner.

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I. IDENTIFICATION OF THE PATENTS

Applicants request that an interference be declared between the instant application and U.S. Patent Nos. 4,968,626 and 5,302,529 to Foster et al ("the Foster '626 Patent" and "the Foster '529 Patent", respectively).

II. PRESENTATION OF PROPOSED COUNT

Attached Appendix A sets forth a proposed Count. The proposed Count is an alternative Count prepared after consideration of the subject matter claimed by the respective parties. The proposed Count contains claim 1 of the instant application, claim 1 of the Foster '626 Patent and claim 1 of the Foster '529 Patent, joined by "or." As defined by the proposed Count, the interfering subject matter of the parties is directed to the cDNA encoding a full length human protein C polypeptide.

Claim 1 of the Foster '626 Patent is included in the proposed Count in accordance with 37 C.F.R. §1.606, which requires:

At the time an interference is initially declared (§1.611), a count shall not be narrower in scope than any application claim that is patentable over the prior art and designated to correspond to the count or any patent claim designated to correspond to the count.

The inclusion of claim 1 of the Foster '626 Patent in the Count is thus in no way an admission of patentability of that claim. Bang reserves the right to challenge the patentability of claim 1 of the Foster '626 Patent during an interference.

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The proposed Count is at least as broad as all of the claims of the Foster '626 Patent and the Foster '529 Patent. In this regard, a part of the proposed Count is identical to claim 1 of the Foster '626 Patent and a part of the proposed Count is identical to claim 1 of the Foster '529 Patent.

An alternative Count is being proposed in part because of the different language utilized by the respective parties to describe the same invention.

III. IDENTIFICATION OF CLAIMS OF THE FOSTER ET AL PATENTS WHICH CORRESPOND TO THE PROPOSED COUNT

Claims 1-3 of the Foster '626 Patent and claims 1-4 of the Foster '529 Patent are believed to correspond to the proposed Count. The proposed Count includes claim 1 of the Bang application, claim 1 of the Foster '626 Patent and claim 1 of the Foster '529 Patent, joined by "or."

Claim 1 of the Foster '626 Patent thus corresponds exactly to one part of the proposed Count. Because of the use of "or," correspondence to one part of the proposed Count is sufficient. Claim 1 of the Foster '626 Patent, as included in the Count, recites an isolated human DNA sequence which encodes a protein having human protein C biological activity. By reference to the specification, such an isolated DNA sequence comprises the sequence as recited in claim 2. Claim 2 of the Foster '626 Patent thus defines the same patentable invention as claim 1. Claim 3 of the Foster '626 Patent defines a "bacterial plasmid or bacteriophage transfer vector

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comprising a cDNA sequence comprising the human protein C gene cDNA sequence." Since the plasmid or vector comprises a cDNA sequence of human protein C, and the proposed Count recites an isolated human DNA sequence which codes for human protein C, this claim also corresponds to the proposed Count. All of the claims of the Foster '626 Patent thus correspond to the proposed Count.

Claim 1 of the Foster '529 Patent corresponds exactly to one part of the proposed Count. Because of the use of "or," correspondence to one part of the proposed Count is sufficient. Claims 2-4 of the Foster '529 Patent further specify the cDNA sequence which the plasmid or vector comprises. The additional plasmids and vectors would be obvious in view of the plasmid or vector of claim 1 of the Foster '529 Patent. Therefore, claims 1-4 of the Foster '529 Patent are directed to the same invention as the proposed Count and correspond to the proposed Count.

IV. CLAIMS OF THE BANG ET AL REISSUE APPLICATION WHICH CORRESPOND TO THE PROPOSED COUNT

Claims 1-80 and 83-92 of the Bang reissue application are believed to correspond to the proposed Count. The proposed Count includes claim 1 of the Bang application, claim 1 of the Foster '626 Patent and claim 1 of the Foster '529 Patent, joined by "or." Bang claim 1 thus corresponds exactly to one part of the proposed Count. Bang claims 2-11, 68, 77, 91 and 92 depend from claim 1 and recite plasmids comprising the DNA of claim 1.

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Independent claim 12 and claims 13-55, 80, 84-87, and 88-90, which depend therefrom, are directed to methods of producing a polypeptide with human protein C activity. These claims thus are directed to the same invention as Bang claim 1 which recites the DNA sequence encoding such a polypeptide. Claims 56-67 recite host cells useful in the claimed methods of producing a polypeptide with human protein C activity. Claims 69-75 are directed to methods of producing human protein C activity in a prokaryotic host cell, employing the DNA of claim 1. Claim 76 is directed to specific plasmids which contain DNA sequences encoding human protein C. Claims 78 and 79 recite specific host cells cultured in the method of claim 72. Bang claim 83 depends from claim 81, and specifies that the DNA sequence comprises the coding sequence for the active heavy chain of human protein C in addition to the coding sequence for the active light chain. Because the claims are all related to the full length DNA sequence encoding human protein C, these claims are all directed to the same invention as claim 1 of the Bang application.

Because of the use of "or," correspondence to one part of the proposed Count is sufficient. The Bang claims of record thus correspond to the proposed Count.

Claims 81 and 82 do not correspond to the proposed Count since they are not directed to the full length DNA sequence encoding human protein C. Instead, these claims are directed to DNA sequences encoding the amino acid sequence of the light chain of human

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protein C. Since the Count is directed to the full length human protein C sequence, claims 81 and 82 are not directed to the invention of the proposed Count

V. APPLICATION OF TERMS OF APPLICATION CLAIMS

Appendix B is a chart providing an element-by-element recitation of the newly added claims of Bang and an indication of the passages in the originally filed application where, at the very least, the claims find support.

VI. EXPLANATION OF HOW THE REQUIREMENT OF 35 U.S.C. §135(b) IS MET

According to 35 U.S.C. §135(b), "[a] claim which is the same as, or for the same or substantially the same subject matter as, a claim of an issued patent may not be made in any application unless such a claim is made prior to one year from the date on which the patent was granted." In the instant case, the Foster '626 Patent issued November 6, 1990, and the Foster '529 Patent issued April 12, 1994. Claim 1 of the Bang Patent issued in U.S. Patent No. 4,775,624 on October 4, 1988, and was originally presented as claim 1 in Application Serial No. 699,967, filed on February 8, 1985. At the very least, claim 1 of the Bang reissue application was present in the Bang Patent and as recited therein is "the same as, or for the same or substantially the same subject matter as, a claim of" the issued Foster Patents and was present prior to one year from the date on which the Foster '626 Patent and Foster '529 Patent issued.

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VII. EXPLANATION OF WHY AN INTERFERENCE SHOULD BE DECLARED

As stated in 37 C.F.R. §1.601(i), "[a]n *interference* is a proceeding instituted in the Patent and Trademark Office before the Board to determine any question of patentability and priority of invention between two or more parties claiming the same patentable invention" [emphasis in original]. According to 37 C.F.R. §1.601(n), "[i]nvention A is the *same patentable invention* as an invention 'B' when invention 'A' is the same as (35 U.S.C. §102) or is obvious (35 U.S.C. §103) in view of invention 'B' assuming invention 'B' is prior art with respect to invention 'A'" [emphasis in original].

Claims 1-3 of the Foster '626 Patent define the same patentable invention as claims 1-4 of the Foster '529 Patent and claims 1-80 and 83-92 of the instant Bang application. All of the claims of the Foster '626 Patent, the Foster '529 Patent and the instant application which should be designated as corresponding to the Count are directed to the isolated DNA sequence encoding a full length human protein C polypeptide. By comparing the sequences disclosed in the instant application to those in the Foster '626 Patent and the Foster '529 Patent, it can be seen that the sequences are substantially the same.

The prosecution histories of the Foster '626 Patent and the Foster '529 Patent also show that these two patents are claiming the same invention as Bang in the instant application. To obtain allowance, the Foster '529 Patent was terminally disclaimed over the Foster '626 Patent in view of an obviousness-type double patenting rejection. Moreover, during prosecution

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of the Foster '626 Patent, the pending claims were rejected under 35 U.S.C. §102(e) and §103 over the Bang Patent which is being reissued by the instant application. These rejections were overcome only by Foster's filing of a Declaration under 37 C.F.R. §1.131.

Because the Bang and Foster claims define the same patentable invention, an interference between claims 1-80 and 83-92 of the Bang application, claims 1-3 of the Foster '626 Patent and claims 1-4 of the Foster '529 Patent should be declared.

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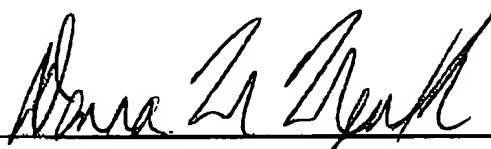
VIII. CONCLUSION

Applicants respectfully request that an interference be declared employing the proposed Count set forth on attached Appendix A with claims 1-80 and 83-92 of the Bang application, claims 1-3 of the Foster '626 Patent and claims 1-4 of the Foster '529 Patent designated as corresponding to the Count. Such action is respectfully requested.

Respectfully submitted,

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By: _____


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Date: August 9, 1999

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A constructed DNA compound that comprises double-stranded deoxyribonucleic acid that encodes a polypeptide with human protein C activity, wherein the coding strand is:

5'-R1 N^{-R}-M-GCC AAC TCC TTC CTG GAG GAG CTC CGT CAC AGC
AGC CTG GAG CGG GAG TGC ATA GAG GAG ATC TGT GAC TTC GAG
GAG GCC AAG GAA ATT TTC CAA AAT GTG GAT GAC ACA CTG GCC
TTC TGG TCC AAG CAC GTC GAC GGT GAC CAG TGC TTG GTC TTG
CCC TTG GAG CAC CCG TGC GCC AGC CTG TGC TGC GGG CAC GGC
ACG TGC ATC GAC GGC ATC GGC AGC TTC AGC TGC GAC TGC CGC
AGC GGC TGG GAG GGC CGC TTC TGC CAG CGC GAG GTG AGC TTC
CTC AAT TGC TCG CTG GAC AAC GGC GGC TGC ACG CAT TAC TGC
CTA GAG GAG GTG GGC TGG CGG CGC TGT AGC TGT GCG CCT GGC
TAC AAG CTG GGG GAC GAC CTC CTG CAG TGT CAC CCC GCA GTG
AAG TTC CCT TGT GGG AGG CCC TGG AAG CGG ATG GAG AAG AAG
CGC AGT CAC CTG AAA CGA GAC ACA GAA GAC CAA GAA GAC CAA
GTA GAT CCG CGG CTC ATT GAT GGG AAG ATG ACC AGG CGG GGA
GAC AGC CCC TGG CAG GTG GTC CTG CTG GAC TCA AAG AAG AAG
CTG GCC TGC GGG GCA GTG CTC ATC CAC CCC TCC TGG GTG CTG

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ACA GCG GCC CAC TGC ATG GAT GAG TCC AAG AAG CTC CTT GTC
AGG CTT GGA GAG TAT GAC CTG CGG CGC TGG GAG AAG TGG GAG
CTG GAC CTG GAC ATC AAG GAG GTC TTC GTC CAC CCC AAC TAC
AGC AAG AGC ACC ACC GAC AAT GAC ATC GCA CTG CTG CAC CTG
GCC CAG CCC GCC ACC CTC TCG CAG ACC ATA GTG CCC ATC TGC
CTC CCG GAC AGC GGC CTT GCA GAG CGC GAG CTC AAT CAG GCC
GGC CAG GAG ACC CTC GTG ACG GGC TGG GGC TAC CAC AGC AGC
CGA GAG AAG GAG GCC AAG AGA AAC CGC ACC TTC GTC CTC AAC
TTC ATC AAG ATT CCC GTG GTC CCG CAC AAT GAG TGC AGC GAG
GTC ATG AGC AAC ATG GTG TCT GAG AAC ATG CTG TGT GCG GGC
ATC CTC GGG GAC CGG CAG GAT GCC TGC GAG GGC GAC AGT GGG
GGG CCC ATG GTC GCC TCC TTC CAC GGC ACC TGG TTC CTG GTG
GGC CTG GTG AGC TGG GGT GAG GGC TGT GGG CTC CTT CAC AAC
TAC GGC GTT TAC ACC AAA GTC AGC CGC TAC CTC GAC TGG ATC
CAT GGG CAC ATC AGA GAC AAG GAA GCC CCC CAG AAG AGC TGG
GCA CCT TAG-3'

wherein

A is deoxyadenyl,

G is deoxyguanyl,

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C is deoxycytidyl,

T is thymidyl,

R is 5'-GCC CAC CAG GTG CTG CGG ATC CGC AAA CGT-3'

or 5'-CAC CAG GTG CTG CGG ATC CGC AAA CGT-3'

R¹ is

5'-ATG TGG CAG CTC ACA AGC CTC CTG CTG TTC GTG

GCC ACC TGG GGA ATT TCC GGC ACA CCA GCT CCT

CTT GAC TCA GTG TTC TCC AGC AGC GAG CGT-3'

or 5'-ATG TGG CAG CTC ACA AGC CTC CTG CTG TTC GTG

GCC ACC TGG GGA ATT TCC GGC ACA CCA GCT CCT

CTT GAC TCA GTG TTC TCC AGC AGC GAG CGT GCC-3'

M is 0 or 1, and

N is 0 or 1,

provided that when M is 0, N must necessarily also be 0 and that when

R is 5'-GCC CAC CAG GTG CTG CGG ATC CGC AAA CGT-3',

R¹ must necessarily be

5'-ATG TGG CAG CTC ACA AGC CTC CTG CTG TTC GTG

GCC ACC TGG GGA ATT TCC GGC ACA CCA GCT CCT

CTT GAC TCA GTG TTC TCC AGC AGC GAG CGT-3';

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and that when

R is 5'-CAC CAG GTG CTG CGG ATC CGC AAA CGT-3',

R¹ must necessarily be

5'-ATG TGG CAG CTC ACA AGC CTC CTG CTG TTC GTG

GCC ACC TGG GGA ATT TCC GGC ACA CCA GCT CCT

CTT GAC TCA GTG TTC TCC AGC AGC GAG CGT GCC-3';

or

an isolated human DNA sequence which codes for a protein having substantially the same biological activity as human protein C;

or

a bacterial plasmid or bacteriophage transfer vector comprising cDNA coding for the amino acid sequence of FIG. 3, starting with alanine, number 1, and ending with proline, number 419, said cDNA sequence coding for human protein C.

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APPENDIX B

APPLICATION OF BANG ADDED CLAIMS TO THE DISCLOSURE OF THE BANG REISSUE APPLICATION

83. The constructed, recombinant DNA sequence of claim 81, further comprising the constructed recombinant DNA sequence that comprises the coding sequence for the active heavy chain of human protein C, said active heavy chain having the amino acid residue sequence:

LEU ILE ASP GLY LYS MET
THR ARG ARG GLY ASP SER PRO
TRP GLN VAL VAL LEU LEU ASP SER
LYS LYS LYS LEU ALA CYS GLY ALA
VAL LEU ILE HIS PRO SER TRP VAL LEU
THR ALA ALA HIS CYS MET ASP
GLU SER LYS LYS LEU LEU VAL ARG
ILE GLY GLU TYR ASP LEU ARG ARG
TRP GLU LYS TRP GLU LEU ASP LEU
ASP ILE LYS GLU VAL PHE VAL HIS
PRO ASN TYR SER LYS SER THR THR
ASP ASN ASP ILE ALA LEU LEU HIS
LEU ALA GLN PRO ALA THR LEU SER
GLN THR ILE VAL PRO ILE CYS LEU
PRO ASP SER GLY LEU ALA GLU ARG
GLU LEU ASN GLN ALA GLY GLN GLU
THR LEU VAL THR GLY TRP GLY TYR
HIS SER SER ARG GLU LYS GLU ALA
LYS ARG ASN ARG THR PHE VAL LEU
ASN PHE ILE LYS ILE PRO VAL VAL
PRO HIS ASN GLU CYS SER GLU VAL
MET SER ASN MET VAL SER GLU ASN
MET LEU CYS ALA GLY ILE LEU GLY
ASP ARG GLN ASP ALA CYS GLU GLY
ASP SER GLY GLY PRO MET VAL ALA
SER PHE HIS GLY THR TRP PHE LEU

Furthermore, the present compounds are easily manipulated to separate the DNA encoding the active human protein C light chain (amino acid residues 43-197) from the DNA encoding the active human protein C heavy chain (amino acid residues 212-461), for the construction of vectors that drive expression of either the light or heavy chain of active human protein C. In this manner, the two chains can be independently produced in suitable, whether eukaryotic or prokaryotic, host cells and then chemically recombined to synthesize active human protein C. (Column 15, lines 30-40).

See also, Sequence in Columns 7 and 8.

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VAL GLY LEU VAL SER TRP GLY GLU
GLY CYS GLY LEU LEU HIS ASN TYR
GLY VAL TYR THR LYS VAL SER ARG
TYR LEU ASP TRP ILE HIS GLY HIS
ILE ARG ASP LYS GLU ALA PRO GLN
LYS SER TRP ALA PRO

wherein ALA is Alanine, ARG is Arginine,
ASN is Asparagine, ASP is Aspartic Acid,
CYS is Cysteine, GLN is Glutamine, GLU is
Glutamic Acid, GLY is Glycine, HIS is
Histidine, ILE is Isoleucine, LEU is Leucine,
LYS is Lysine, MET is Methionine, PHE is
Phenylalanine, PRO is Proline, SER is Serine,
THR is Threonine, TRP is Tryptophan, TYR
is Tyrosine, and VAL is Valine.

84. The method of claim 12,
further comprising isolating said polypeptide
with human protein C activity.

Those skilled in the art will
recognize that the expression vectors of this
invention are used to transform either
eukaryotic or prokaryotic host cells, such
that a polypeptide with human protein C
activity is expressed by the host cell. If the
host cell is transformed with a vector
comprising a promoter that functions in the
host cell and drives transcription of the
nascent human protein C structural gene,
and if the host cell possesses the cellular
machinery with which to process the signal
peptide, protein C activity can be isolated
from the media. Under other expression
conditions, such as when plasmid pCZ460 is
in *E. coli* RV308, the protein C activity must
be isolated from the host cell. (Column 18,
lines 53-63).

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85. The method of claim 84, wherein said polypeptide is human protein C zymogen.

Human protein C is a serine protease zymogen present in blood plasma and synthesized in the liver. (Column 2, lines 65-66).

Zymogen - an enzymatically inactive precursor of a proteolytic enzyme. (Column 4, lines 46-47).

86. The method of claim 85 which further comprises activating the human protein C zymogen to produce human activated protein C.

The activation of the zymogen into the active serine protease involves the proteolytic cleavage of an ARG-LEU peptide bond (residues 211 and 212). This latter cleavage releases a dodecapeptide (residues 200-211) constituting the amino-terminus of the larger chain of the two-chain molecule. (Column 3, lines 10-15),

87. A method of claim 86, wherein the activation step is performed using a thrombomodulin-thrombin complex.

Protein C zymogen or activated protein C is useful in the treatment of disseminated intravascular coagulation. As mentioned above, the levels of protein C in disseminated intravascular coagulation are severely reduced, probably through a mechanism which involves the widespread activation of the protein by thrombomodulin-thrombin and the subsequent catabolism or inactivation of the activated enzyme. (Column 20, lines 53-60).

The activation [of Protein C Zymogen] makes use of rabbit thrombomodulin complexed with bovine thrombin; the complex is immobilized on agarose beads. (Column 55, lines 43-45).

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88. The method of claim 12, wherein said recombinant DNA vector is a eukaryotic vector.

As stated above, a variety of recombinant DNA expression vectors comprising the protein C activity-encoding DNA have been constructed. The present vectors are of two types: those designed to transform eukaryotic, especially mammalian, host cells; and those designed to transform *E. coli*. (Column 9, lines 46-51).

89. The method of claim 88, wherein said eukaryotic vector is a mammalian vector.

As stated above, a variety of recombinant DNA expression vectors comprising the protein C activity-encoding DNA have been constructed. The present vectors are of two types: those designed to transform eukaryotic, especially mammalian, host cells; and those designed to transform *E. coli*. (Column 9, lines 46-51).

90. The method of claim 12, wherein said eukaryotic host cell is a mammalian host cell.

Those skilled in the art will recognize that the expression vectors of this invention are used to transform either eukaryotic or prokaryotic host cells, such that a polypeptide with human protein C activity is expressed by the host cell. If the host cell is transformed with a vector comprising a promoter that functions in the host cell and drives transcription of the nascent human protein C structural gene, and if the host cell possesses the cellular machinery with which to process the signal peptide, protein C activity can be isolated from the media. Under other expression conditions, such as when plasmid pCZ460 is in *E. coli* RV308, the protein C activity must be isolated from the host cell. (Column 18, lines 53-63).

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91. The plasmid of claim 2, further comprising a murine dihydrofolate reductase (dhfr) gene under the control of an SV40 early promoter.

Plasmid pSV2-dhfr (ATCC 37146) comprises a murine dihydrofolate reductase (dhfr) gene under the control of an SV40 early promoter. Under the appropriate conditions, the dhfr gene is known to be amplified, or copies, in the host chromosome. (Column 11, lines 11-15).

92. The plasmid of claim 2, further comprising a promoter selected from the group consisting of an SV40 early promoter and an SV40 late promoter.

Illustrative plasmids of the present invention which were constructed for expression of protein C activity in mammalian and other eukaryotic host cells also utilize promoters other than the SV40 early promoter. . . . Other promoters, such as the SV40 late promoter . . . can be readily isolated and modified for use on recombinant DNA expression vectors designed to produce protein C in eukaryotic host cells. (Column 11, lines 34-48).

BURNS, DOANE, SWECKER & MATHIS, L.L.P.
ATTORNEYS AT LAW

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of)	
U.S. Patent No. 4,775,624)	
)	
Nils U. Bang et al)	
)	Group Art Unit: Unassigned
)	
Application No.: Unassigned)	Examiner: Unassigned
)	
Filed: November 4, 1998)	
)	
For: VECTORS AND COMPOUNDS FOR)	
EXPRESSION OF HUMAN)	
PROTEIN C)	

TRANSMITTAL LETTER FOR APPLICATION
FOR REISSUE OF UNITED STATES UTILITY PATENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Transmitted herewith for filing is an application for reissue of United States Letters Patent No. 4,775,624, issued on October 4, 1998, to Niles U. Bang et al, and assigned of record to Eli Lilly and Company.

Enclosed herewith are the following documents:

- a copy of the original Letters Patent No. 4,775,624, together with new claims;
- Declaration Under 37 C.F.R. §1.175(a);
- Certificate Under 37 C.F.R. §3.73(b);
- Notification Pursuant to 37 C.F.R. §1.607(c);
- Request for Transfer of Formal Drawings; and

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- Power of Attorney By Assignee of Entire Interest.

Also enclosed is the filing fee of \$790.00, plus an additional \$1,584.00 for 72 additional dependent claims in excess of twenty, as required by 37 C.F.R. §1.16(h)-(j).

It is requested that all future correspondence relating to this application for reissue of United States Patent No. 4,775,624 be addressed to:

R. Danny Huntington
Burns, Doane Swecker & Mathis, L.L.P.
P.O. Box 1404
Alexandria, Virginia 22313-1404.

Please address all telephone calls to R. Danny Huntington.

The Commissioner is hereby authorized to charge any appropriate fees under 37 C.F.R. §§1.16, 1.17 and 1.21 that may be required by this paper, and to credit any overpayment to Deposit Account No. 02-4800. This paper is submitted in triplicate.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

By: R. Danny Huntington
R. Danny Huntington
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Date: November 4, 1998